ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 U insulin glulisine (equivalent to 3.49 mg).

Each vial contains 10 ml of solution for injection, equivalent to 1000 U.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in vial.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

Apidra must not be mixed with any preparations other than NPH (Neutral Protamine Hagedorn) human insulin.

Continuous subcutaneous infusion pump

When used with an insulin infusion pump, Apidra must not be mixed with diluents or any other insulin.

For further details on handling, see section 6.6

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and special precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine
in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisineis excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: >1/10; common: >1/100, <1/10; uncommon: > 1/1,000, < 1/100; rare: >1/10,000, <1/1,000; very rare: < 1/10,000).

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

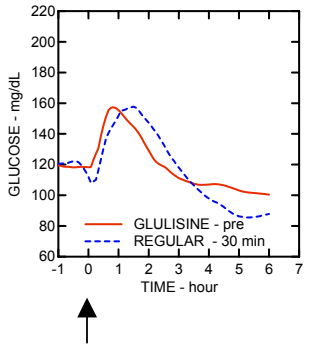

Figure 1 A

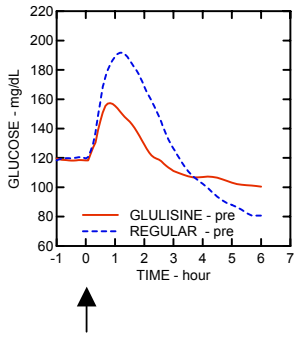

Figure 1B

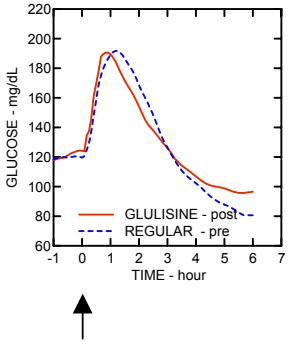

Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

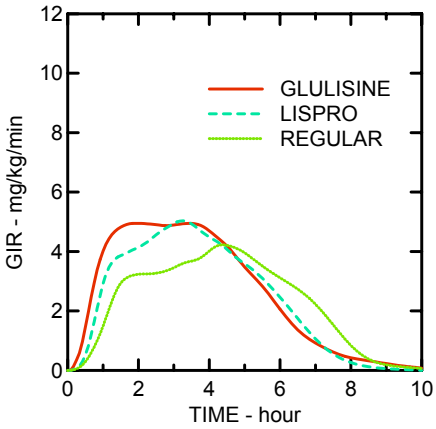

Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Clinical studies

Type 1 diabetes mellitus
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 2 diabetes mellitus
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and Gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µU/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µU/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure3).

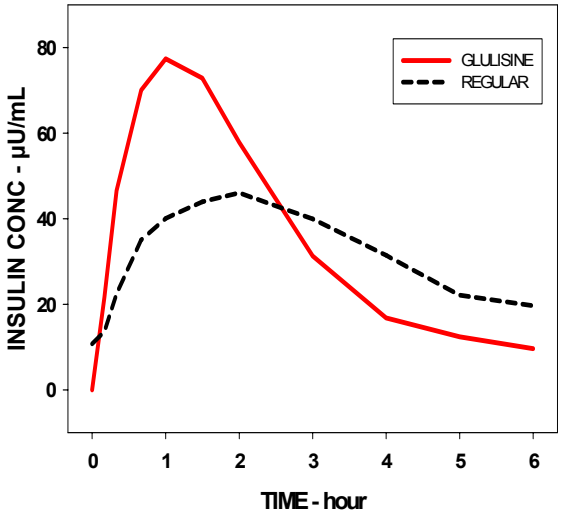

Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellituspatients after a dose of 0.15 U/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the Cmax was 91 µU/ml with the interquartile range from 78 to 104 µU/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similarbetween injection sites and of low intra-subject variability (11%CV).

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.
After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control

than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Preclinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with any preparations other than NPH human insulin.

When used with an insulin infusion pump, Apidramust not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Shelf life after first use
4 weeks.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Colourless glass vial (type I) with flanged aluminium overseal, elastomeric rubber stopper and tear-off lid. Each vial contains 10 ml solution. Packs of 1, 2, 4 and 5 vials are available.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system (see section 4.2).

Inspect the vial before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Since Apidra is a solution, it does not require resuspension before use.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

Continuous subcutaneous infusion pump

Apidra may be used for Continuous Subcutaneous Insulin Infusion (CSII)in pump systems suitable for insulin infusion with the appropriate catheters and reservoirs.

Patients using CSII should be comprehensively instructed on the use of the pump system. The infusion set and reservoir should be changed every 48 hours using aseptic technique.

Patients administering Apidra by CSII must have alternative insulin available in case of pump system failure.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in cartridge.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 U insulin glulisine (equivalent to 3.49 mg).

Each cartridge contains 3 ml of solution for injection, equivalent to 300 U.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

Apidra must not be mixed with any preparations other than NPH (Neutral Protamine Hagedorn) human insulin.
For further details on handling, see section 6.6

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisinehave not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.5 Special warnings and special precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.9 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: >1/10; common: >1/100, <1/10; uncommon: > 1/1,000, < 1/100; rare: >1/10,000, <1/1,000; very rare: < 1/10,000).

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.
There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:
Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.
Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

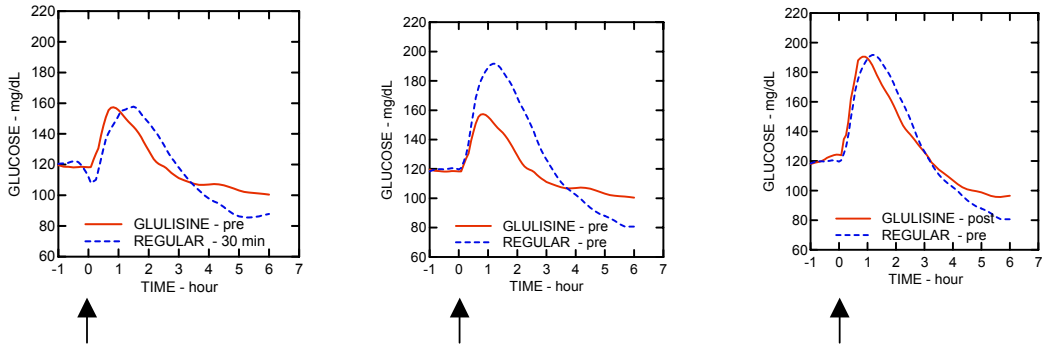

Figure 1 A Figure 1B Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

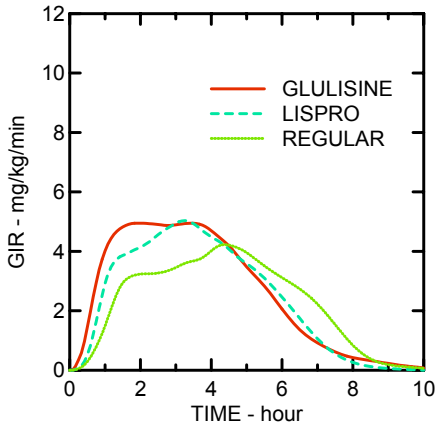

Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Clinical studies

Type 1 diabetes mellitus
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 2 diabetes mellitus
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and Gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µU/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µU/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

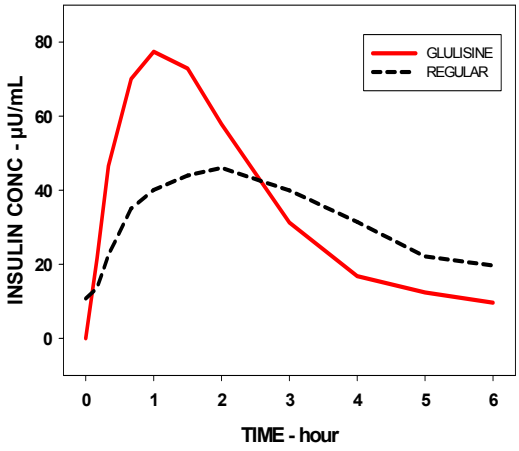

Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 U/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the Cmax was 91 µU/ml with the interquartile range from 78 to 104 µU/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similarbetween injection sites and of low intra-subject variability (11%CV).

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.
After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Preclinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with any preparations other than NPH human insulin.

6.3 Shelf life

2 years.
Shelf life after first use
4 weeks.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C) .
Keep the cartridge in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Keep the cartridge in the outer carton in order to protect from light.

6.5 Nature and contents of container

Colourless glass cartridge (type I) with elastomeric rubber plunger and flanged aluminium overseal with elastomeric rubber stopper. Each cartridge contains 3 ml . Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges are available.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

The cartridges are to be used in conjunction with an insulin pen such as OptiPen and as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.Inspect the cartridge before use. It must

only be used if the solution is clear, colourless, with no solid particles visible. Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

If OptiPen is damaged, it should not be used.

If the pen malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 U/ml) and injected.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/005-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in cartridge.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 U insulin glulisine (equivalent to 3.49 mg).

Each cartridge contains 3 ml of solution for injection, equivalent to 300 U.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge for OptiClik.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

Apidra must not be mixed with any preparations other than NPH (Neutral Protamine Hagedorn) human insulin.

For further details on handling, see section 6.6

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and special precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: >1/10; common: >1/100, <1/10; uncommon: > 1/1,000, < 1/100; rare: >1/10,000, <1/1,000; very rare: < 1/10,000).

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

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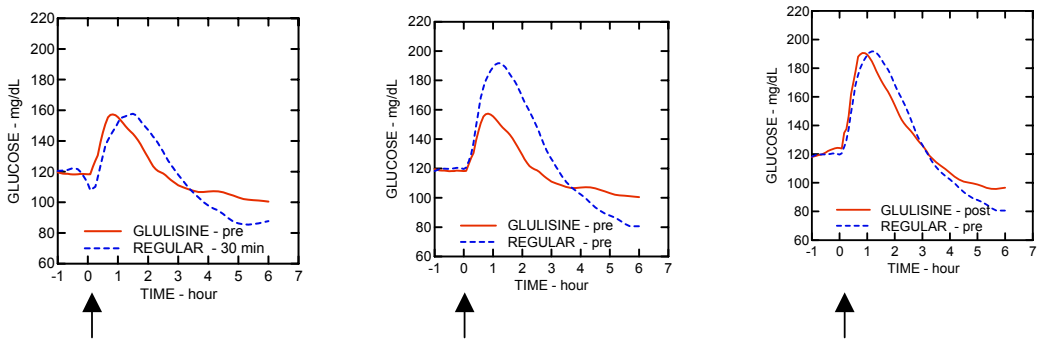

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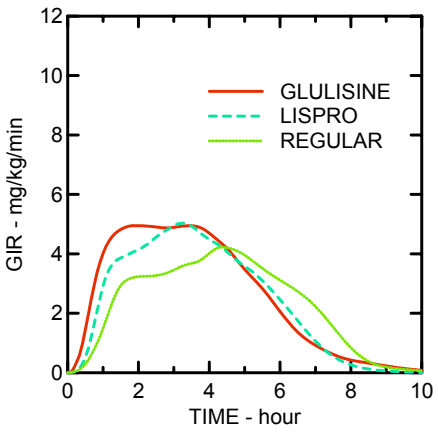

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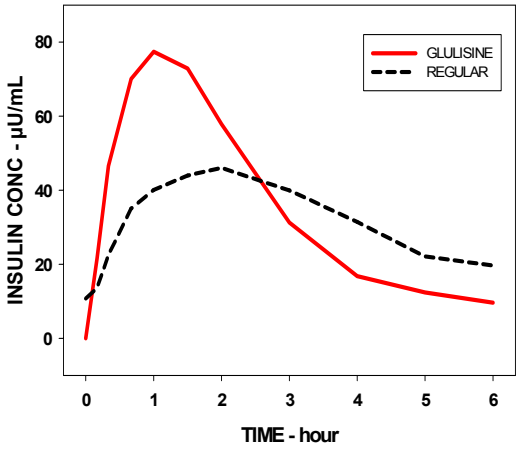

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6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C).
Keep the cartridge in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Keep the cartridge in the outer carton in order to protect from light.

6.5 Nature and contents of container

Colourless glass cartridge (type I) with elastomeric rubber plunger and flanged aluminium overseal with elastomeric rubber stopper. Each cartridge contains 3 ml.

The glass cartridge is irreversibly integrated in a transparent container and attached to a plastic mechanism by a threaded rod at one extremity.

Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges for OptiClik are available. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

The cartridges for OptiClik are to be used in conjunction with OptiClik only, and as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used.

Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Inspect the cartridge before use. It must only be used if the cartridge is intact and the solution is clear, colourless, with no solid particles visible.
Air bubbles must be removed from the cartridge before injection (see instruction for using pen).
Empty cartridges must not be refilled.

If the pen malfunctions,(see instructions for using the pen) the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 U/ml) and injected.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/021-028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 U insulin glulisine (equivalent to 3.49 mg).

Each pen contains 3 ml of solution for injection, equivalent to 300 U.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen. OptiSet.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables., Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

Apidra must not be mixed with any preparations other than NPH (Neutral Protamine Hagedorn) human insulin.

Before using OptiSet, the Instructions for Use included in the Package Leaflet must be read carefully (see 6.6).

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and special precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

Handling of the pen
Before using OptiSet, the Instructions for Use included in the Package Leaflet must be read carefully. OptiSet has to be used as recommended in these Instructions for Use (see 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data onthe use of insulin glulisine
in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisineis excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: >1/10; common: >1/100, <1/10; uncommon: > 1/1,000, < 1/100; rare: >1/10,000, <1/1,000; very rare: < 1/10,000).

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

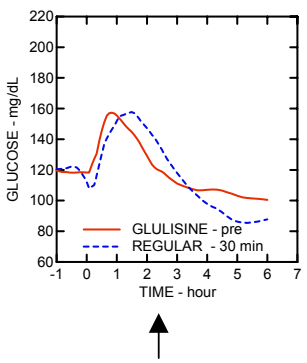


Figure 1 A

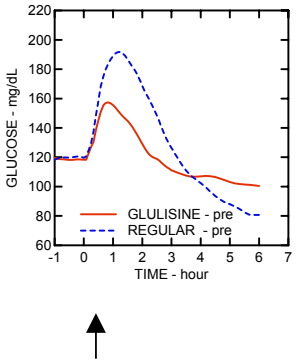


Figure 1B

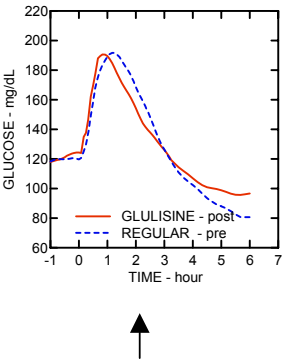


Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

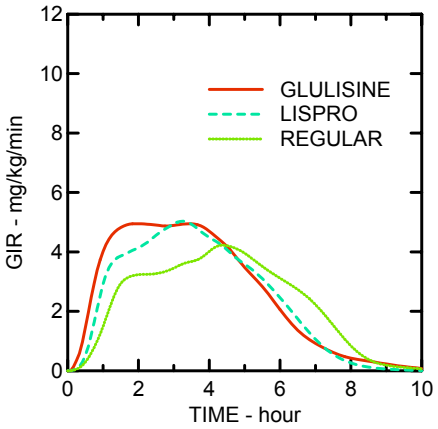


Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Clinical studies

Type 1 diabetes mellitus
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 2 diabetes mellitus
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and Gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 □U/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 □U/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure3).

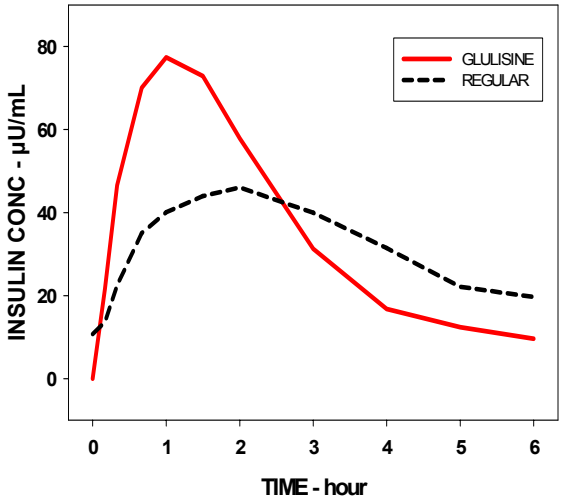


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 U/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the Cmax was 91 µU/ml with the interquartile range from 78 to 104 µU/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similarbetween injection sites and of low intra-subject variability (11%CV).

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.
After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control

than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Preclinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with any preparations other than NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use
4 weeks.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C) .
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not refrigerate.

6.5 Nature and contents of container

Colourless glass cartridge with elastomeric rubber plunger and flanged aluminium overseal with elastomeric rubber stopper. Each pen contains 3 ml solution . The cartridges are sealed in a disposable pre-filled pen. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pens are available.

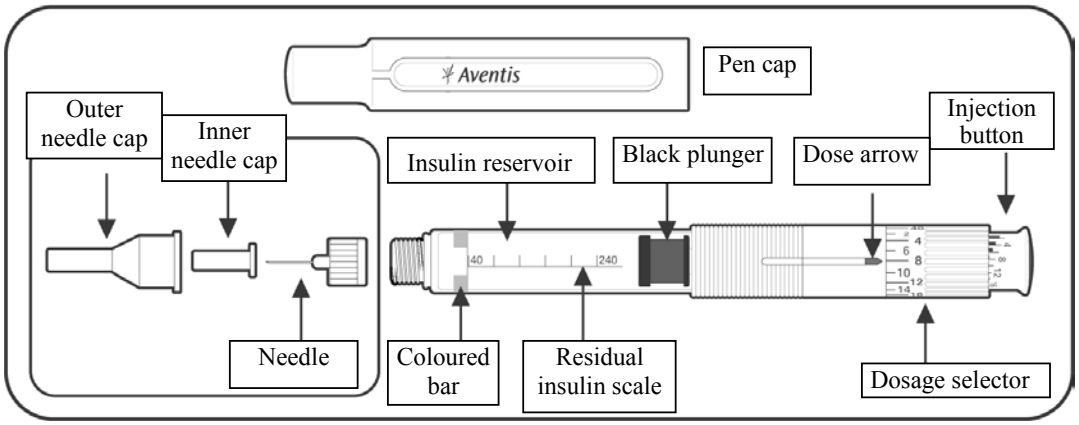
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Apidra is a solution, it does not require resuspension before use.

Empty pens must never be used and must be properly discarded.
To prevent any kind of contamination, the use of the pre-filled pen should remain strictly for a single patient use.

Handling of the pen
The Instructions for Use included in the Package Leaflet must be read carefully before using OptiSet.



Schematic diagram of the pen

Important information for use of OptiSet:
- Before use, a new needle must always be carefully attached and a safety test must be performed.
- The dosage selector must never be turned after the injection button has been pulled out.
- If a problem occurs with OptiSet, the section "Troubleshooting" in the User Manual should be referred to.
- If OptiSet is damaged, or not working properly (due to mechanical defects) it has to be discarded and a new OptiSet has to be used

General Notes
- The injection button allows checking the actual loaded dose: The button should be pulled out. While holding it out, the last thick bar visible (only the top part can be seen) shows the amount of insulin loaded. If it is difficult to see, the pen may be held at an angle.
- The insulin pen must not be dropped or subjected to impact ,otherwise, the insulin cartridge in the transparent insulin reservoir may break and the pen will not work. If this happens, a new pen must be used.

Step 1 Check the Insulin

After removing the pen cap, the label on the insulin reservoir should be checked to make sure it contains the correct insulin. The appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency.

.

Step 2 Attaching the needle

Only needles that have been approved for use with OptiSet may be used.
After removing the pen cap, the needle should be carefully attached straight onto the pen.

Step 3 Safety test

Prior to each injection a safety test has to be performed.

For a new and unused OptiSet, the dose arrow should point to the number 8, as preset by the manufacturer.

Otherwise, the dosage selector should be turned until the dose arrow points to 2. Then the injection button should be pulled out as far as it will go.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.
If insulin has been expelled through the needle tip, then the pen and the needle are working properly.
If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4 Setting and loading the insulin dose

The dose can be set in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If a dose greater than 40 units is required, it should be given as two or more injections.

The dosage selector should be turned in either direction until the dose arrow points to the required dose.

The injection button should be pulled out as far as it will go in order to load the pen.

Step 5 Injecting the insulin dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin

The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

.**Step 6 Removing the needle**

The needle should be removed after each injection and discarded. This will prevent contamination as well as leakage, re-entry of air and potential needle blocks. Needles must not be reused.

The pen cap should be replaced on the pen.

Checking the reservoir for remaining insulin

The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.

The actual loaded dose should be checked as per “General notes”.In case, the patient is not sure whether enough insulin remains in the reservoir, the OptiSet should be discarded.
*Example:*If the dose arrow has been set to 30 units and injection button can only be pulled out to as far as 12 units, then only 12 units insulin can be injected with this pen. In this example, either the other 18 units will have to be injected using a new pen, or the entire 30 units dose will have to be injected using a new pen.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/013-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Aventis Pharma Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

Name and address of the manufacturer responsible for batch release

Aventis Pharma Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in vial
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.
One vial of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
After first use: Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in vial
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.
Two vials of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
After first use: Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/002

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in vial
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.
Four vials of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
After first use: Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/003

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 U/ml, solution for injection in vial
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.
Five vials of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
After first use: Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/004

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100U/ml
Solution for injection in vial
Insulin glulisine.

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
One cartridge of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/005

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Three cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/006

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Four cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/007

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Five cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/008

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Six cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/009

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Eight cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/010

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Nine cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/011

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Ten cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/012

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100U/ml
Solution for injection in cartridge.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

2. METHOD OF ADMINISTRATION

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
One cartridge of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/021

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Three cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/022

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Four cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/023

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Five cartridges of 3ml
Use only clear and colourless solutions.
Read enclosed leaflet before use.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/024

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Six cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/025

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Eight cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/026

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Nine cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/027

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100U/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
Ten cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/028

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL for OptiClik

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100U/ml
Solution for injection in cartridge.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
One pen of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/013

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Three pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/014

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Four pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/015

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Five pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/016

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Six pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/017

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Eight pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time let fully before using OptiSet.

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/018

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Nine pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time let fully before using OptiSet.

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/019

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NOT OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 U (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. OptiSet.
Ten pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keepthe pre-filled pen in the outer carton in order to protect from light.

After first use: Do not store above 25°C and do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/020

13. MANUFACTURER'S BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra , 100 U/ml.
Solution for injection in pre-filled pen. OptiSet.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally, and you should not give it to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Apidra 100 U/ml solution for injection in vial.
Insulin glulisine.

- The active substance is insulin glulisine. One millilitre of the solution contains 100 U (Units) of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

The marketing authorisation holder is:
Aventis Pharma Deutschland GmbH
Brüningstraße 50, D-65926 Frankfurt am Main
Germany.

The manufacturer is:
Aventis Pharma Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Each vial contains 10 ml solution (1000 U). Packs of 1, 2, 4 and 5 vials of 10 ml are available.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if:
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic to insulin glulisine or any of the other ingredients contained in Apidra.

Take special care with Apidra:

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines:

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:

- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

Taking/using other medicines:

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Tell your doctor about all medicines that you are taking, including those you have bought without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensin converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g. asprin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill

used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long -acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle the vials

Look at the vial before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system.

If you have to mix two types of insulin

Apidra must not be mixed with any preparation other than NPH human insulin.

If Apidra is mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing.

How to handle an infusion pump system

Apidra must never be mixed with diluents or any other insulin when used in a pump.

Before use of Apidra in the pump system you should have received comprehensive instructions of this use. In addition, information about any action to be taken in case of illness, too high or too low blood sugar or failure of the pump system.

Use the type of pump system recommended by your doctor. Read and follow the instructions that accompany your insulin infusion pump. Follow your doctor's instructions about the basal infusion rate and the mealtime insulin boluses to be taken. To get the benefit of insulin infusion, and to detect possible malfunction of the insulin pump, you should measure your blood sugar level regularly.

The infusion set and reservoir should be changed every 48 hours using aseptic technique.

What to do in case of pump system failure ?

You should always have alternative insulin available for injection under the skin in case of pump system failure.

If you take more Apidra than you should:

If you **have injected too much Apidra**,your blood sugar may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra:

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further recommendationson hyperglycaemia.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can have side effects.

Hypoglycaemia (low blood sugar) this means that there is not enough sugar in the blood

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Hyperglycaemia (high blood sugar) this means that there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Skin side-effects and allergic reactions
If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Systemic allergy, less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Tell your doctor or pharmacist if you notice any of the side-effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side-effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too <u>high</u> (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high:
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too <u>low</u> (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels) are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.
Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING APIDRA

Unopened
Store in a refrigerator (2°C – 8°C),
Do not freeze.
Ensure that the vial is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Do not refrigerate.

Once in use, it can be kept for up to 4 weeks and it is recommended that the date of first use from the vial be noted on the label.

Keep the vial in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and carton.

Do not use Apidra if it does not appear clear and colourless.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

PACKAGE LEAFLET

Before you start using this medicine please read carefully all of this leaflet and the instructions for using the pen provided with your insulin pen.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally, and you should not gives it to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Apidra 100 U/ml solution for injection in cartridge.
Insulin glulisine.

- The active substance is insulin glulisine. One millilitre of the solution contains 100 U (Units) of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

The marketing authorisation holder is:
Aventis Pharma Deutschland GmbH
Brüningstraße 50, D-65926 Frankfurt am Main
Germany.

The manufacturer is:
Aventis Pharma Deutschland GmbH
Industriepark Höchst, D- 65926 Frankfurt
Germany

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Each cartridge contains 3 ml solution (300 U). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges of 3 ml are available.
Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if:
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic to insulin glulisine or any of the other ingredients contained in Apidra.

Take special care with Apidra:

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents..

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines:

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

Taking/using other medicines:

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Tell your doctor about all medicines that you are taking, including those you have bought without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensine converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g. aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle the cartridge

Look at the cartridge before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

The cartridges are to be used in conjunction with an insulin pen such as OptiPen as recommended in the information provided by the device manufacturer.

The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection

Before insertion of the cartridge into the reusable pen OptiPen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen).. Empty cartridges must not be refilled.

Never use OptiPen if it is damaged or if you are not sure that it is working properly.

To prevent any kind of contamination, the reusable pen should be used only by you.

If the pen malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 IU/ml) and injected.

If you take more Apidra than you should:

If you **have injected too much Apidra**,your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra:

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further recommendationson hyperglycaemia.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can have side effects.

Hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Hyperglycaemia (high blood sugars) this means that there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Skin side-effects and allergic reactions

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Systemic allergy, less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Tell your doctor or pharmacist if you notice any of the side-effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side-effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too <u>high</u> (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too <u>low</u> (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels)are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in

concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.

Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING APIDRA

Unopened
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Do not refrigerate.

Once in use, it should be kept for up to 4 weeks.

Keep the cartridge in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and carton.

Do not use Apidra if it does not appear clear and colourless.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

PACKAGE LEAFLET

Before you start using this medicine, please read carefully all of this leaflet. The instructions for using OptiClik, the insulin pen, are provided with your OptiClik. Please refer to them before using your medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally, and you should not gives it to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Apidra 100 U/ml solution for injection in cartridge.
Insulin glulisine.
This cartridge is for use with OptiClik only.

- The active substance is insulin glulisine. One millilitre of the solution contains 100 U (Units) of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

The marketing authorisation holder is:
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Germany.

The manufacturer is:
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Industriepark Höchst, D- 65926 Frankfurt
Germany

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Each cartridge contains 3 ml solution (300 U). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if:

- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic to insulin glulisine or any of the other ingredients contained in Apidra.

Take special care with Apidra:

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents..

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines:

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:

- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

Taking/using other medicines:

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Tell your doctor about all medicines that you are taking, including those you have bought without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensine converting enzyme (ACE) inhibitors (used for the treatment of certain heart

conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g. aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle the cartridge for OptiClik

Look at the cartridge before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

Apidra in cartridge for OptiClik has been developed for use in OptiClik only.The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection

Before insertion of the cartridge into the reusable pen OptiClik the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen).. Empty cartridges must not be refilled.

Problems with OptiClik?

Please refer to the manufacturer's instructions for using the pen.
If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used.

To prevent any kind of contamination, the reusable pen should be used only by you.

If the OptiClik does not function well, you can draw the insulin from the cartridge into a syringe for injection. Therefore, keep syringes and needles as well. However, use only syringes which are designed for an insulin concentration of 100 IU (Units) per millilitre.

If you take more Apidra than you should:

If you **have injected too much Apidra**,your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra:

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further recommendationson hyperglycaemia.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can have side effects.

Hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Hyperglycaemia (high blood sugars) this means that there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Skin side-effects and allergic reactions

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Systemic allergy, less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Tell your doctor or pharmacist if you notice any of the side-effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too <u>high</u> (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too <u>low</u> (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels)are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,

- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.

Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING APIDRA

Unopened
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
Do not store above 25°C.
Do not refrigerate.

Once in use, it should be kept for up to 4 weeks.

Keep the cartridge in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and carton.

Do not use Apidra if it does not appear clear and colourless.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

PACKAGE LEAFLET

Before you start using this medicine, please carefully read all of this leaflet including the Instructions for Use of OptiSet.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally, and you should not give it to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Apidra 100 U/ml, solution for injection in pre-filled pen. OptiSet.
Insulin glulisine.

- The active substance is insulin glulisine. One millilitre of the solution contains 100 U (Units) of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

The marketing authorisation holder is:
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The manufacturer is:
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1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Each pen contains 3 ml solution (300 U). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pre-filled pens of 3 ml are available.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if:
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic to insulin glulisine or any of the other ingredients contained in Apidra.

Take special care with Apidra:

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines:

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

Taking/using other medicines:

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Tell your doctor about all medicines that you are taking, including those you have bought without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensin converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g.aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline]or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle OptiSet

OptiSet is a pre-filled disposable pen containing insulin glulisine.

Read carefully the " OptiSet Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Before use always attach a new needle, and perform a safety test. Only use needles that have been approved for use with OptiSet.

Look at the cartridge sealed in the disposable pen injector before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with OptiSet, please refer to the Troubleshooting section of the attached OptiSet Instructions for Use, or have it checked by your doctor or pharmacist.

If you take more Apidra than you should:

If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra:

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further information on hyperglycaemia.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can have side effects.

Hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Hyperglycaemia (high blood sugars) this means there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Skin side-effects and allergic reactions

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Systemic allergy, less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Tell your doctor or pharmacist if you notice any of the side-effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side-effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too high (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too low (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low bllod sugar levels) are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.
Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING APIDRA

Unopened
Store in a refrigerator (2°C - 8°C).
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not freeze.
Ensure that the pre-filled pen is not directly touching the freezer compartment or freezer packs.

In use conditions
Do not store above 25°C.
Do not refrigerate.
Once in use, it should be kept for up to 4 weeks.

Keep the pre-filled pen in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and carton.

Do not use Apidra if it does not appear clear and colourless.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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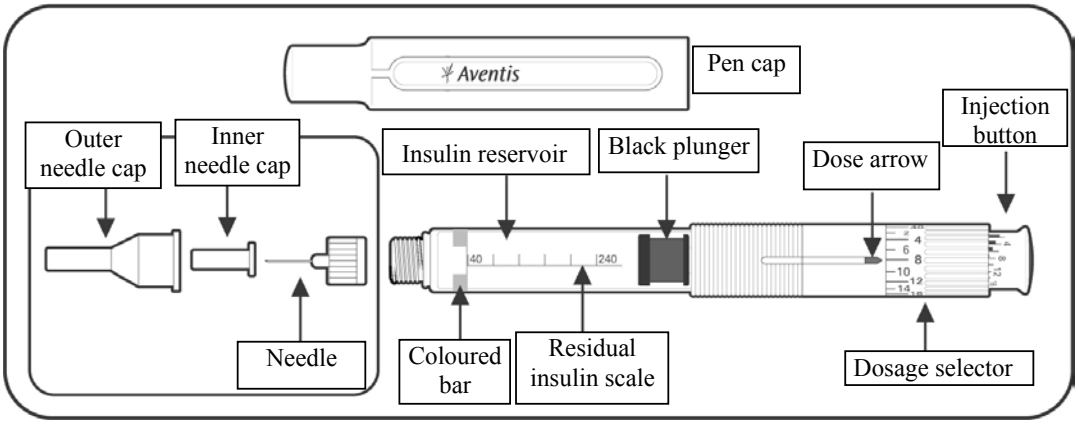
This leaflet was last approved on {date}

OptiSet INSTRUCTIONS FOR USE

Please read these Instructions for Use carefully and completely before using OptiSet for the first time. Keep this leaflet for future reference for each time you use OptiSet.



Schematic diagram of the pen

Important information for use of OptiSet:

- . A new needle must be attached before each use (see step 2).
- A safety test must be performed before each injection (see step 3).
- Never turn the dosage selector (change the dose) after injection button has been pulled out.
- This pen is for your use only, do not share it with anyone else.
- If a problem occurs with OptiSet please refer to the section "Troubleshooting".
- Never use OptiSet if it is damaged or if you are not sure that it is working properly.

Step 1 Check your Insulin

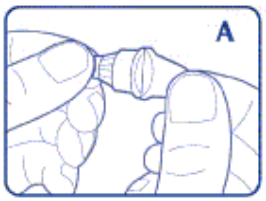
Remove the pen cap.

Check the label on the insulin reservoir to make sure you have the correct insulin.
Check the appearance of your insulin. The insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency.

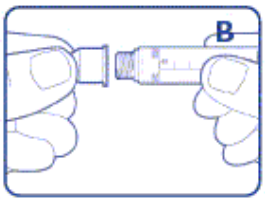
Step 2 Attaching the needle

Attach a new needle before use.
Only use needles that have been approved for use with OptiSet.

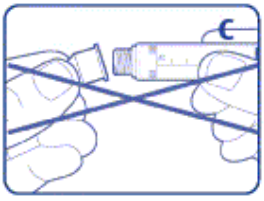
A Remove the protective tab from the needle container



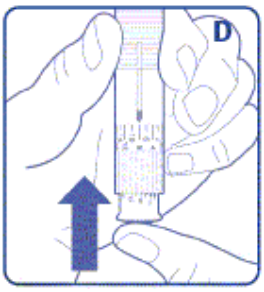
B Carefully attach the needle, together with the outer needle cap, **straight** onto the pen (screw or push on, depending on the needle type).



C Do not attach the needle at a slant. This may cause it to break or lead to leakage and incorrect dosing. Do not force the needle.



D Make sure the injection button is pressed in.



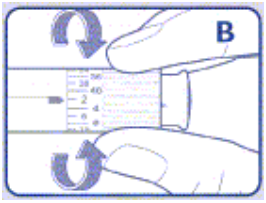
Step 3 Safety test

Prior to each injection a safety test has to be performed.
Always attach a new needle before performing the safety test.

If you are using a new and unused OptiSet, you should use a dose of 8 units, already preset by the manufacturer, for the first safety test. Follow step A.
Otherwise, you should set a dose of 2 units for the safety test. Follow step B

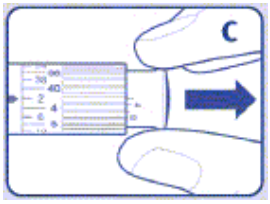
A For new and unused OptiSet only: Check that the dose arrow is pointing to the number 8. If that is not the case use a new OptiSet.
Now go directly to step C.

B For an OptiSet already in use: Turn the dosage selector until the dose arrow points to 2 (The dosage selector may be turned in either direction.).



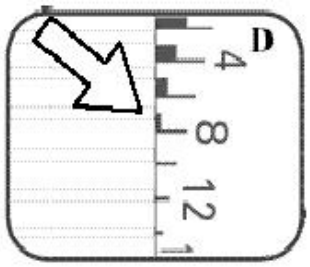
C Pull the injection button out as far as it will go.

Never turn the dosage selector once the injection button has been pulled out.

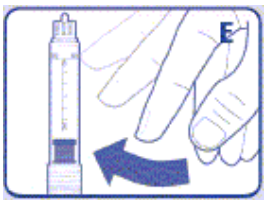


D Check if the numbers on the injection button match with the dose you chose on the dosage selector:

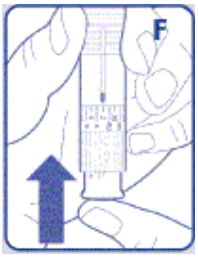
- Black lines show the number of units. These lines changes from thin to thick
- Pull out the button completely and hold it out.
- The last thick bar visible (only the top part can be seen) shows the amount of insulin loaded. You may need to turn the pen to see the last thick bar.
- If it is difficult to see, you can hold the pen at an angle.
- In this picture, 8units are loaded



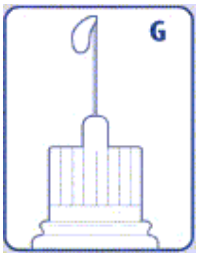
E Remove the outer and inner needle caps. Hold the pen with the needle pointing upwards and tap the insulin reservoir gently with the finger so that any air bubbles rise up towards the needle



F Press in the injection button completely, to expel the dose. A clicking sound can be heard, which will stop when the injection button has been pressed completely



G If insulin has been expelled through the needle, then your pen and the needle are working properly.



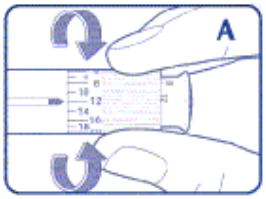
If no insulin appears at the needle tip, repeat the safety test (steps 3B-G) until it does.

If no insulin is expelled from the needle even after the safety test has been repeated, check for air bubbles:
If air bubbles are present repeat Safety test until air bubbles are removed.
If no air bubbles are present the needle may be blocked. Please change the needle.

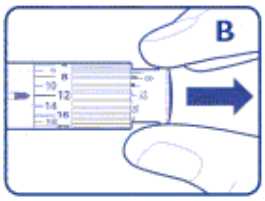
Step 4 Setting and loading the insulin dose

You can set the dose in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If you need a dose greater than 40 units, you should give it as two or more injections.

A Turn the dosage selector in either direction until the dose arrow points to the required dose.

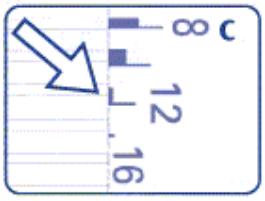


B Pull out the injection button as far as it will go in order to load the dose.



Never turn the dosage selector once the injection button has been pulled out.

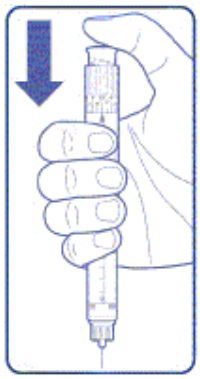
C Check if the numbers on the injection button match with the dose you chose on the dosage selector:
- Black lines show the number of units. These lines change from thin to thick.
- Pull out the button completely and hold it out.
- The last thick bar visible (only the top part can be seen) shows the amount of insulin loaded. You may need to turn the pen to see the last thick bar
- If it is difficult to see, you can hold the pen at an angle.
- In this example, 12 units is loaded



Step 5. Injecting the insulin dose

Use the injection technique as advised by your health care professional.
Insert the needle into the skin

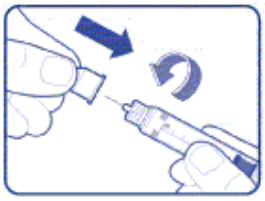
Press in the injection button completely. A clicking sound can be heard, which will stop when the injection button has been pressed completely. Then slowly count to 10 while holding down the injection button before withdrawing the needle. This ensures that the full dose of insulin has been injected.



Step 6 Removing the needle

To avoid injuries replace only the outer needle cap onto the needle. Unscrew the needle by turning the needle cap Dispose of the used needle safely.

Remove the needle after each injection and discard it. This will prevent contamination as well as leakage, air and potential needle blocks. Needles must not be reused.

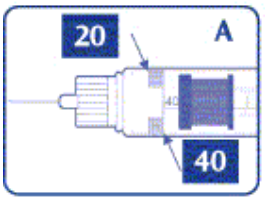


Now replace the pen cap on the pen.

Checking the reservoir for remaining insulin

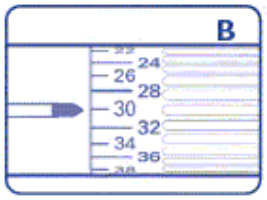
The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.

A If the black plunger is at the beginning of the coloured bar, then there are approximately 40 units of insulin available. If the black plunger is at the end of the coloured bar, then there are approximately 20 units of insulin available

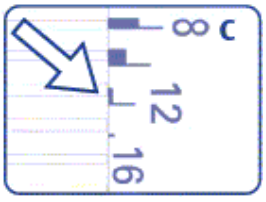


When the level of insulin in the reservoir is low, the injection button allows you to check the dose:
- Black lines show the number of units. These lines change from thin to thick.
- Pull out the button completely and hold it out.
- The last thick bar visible (only the top part can be seen) shows the amount of insulin loaded. You may need to turn the pen to see the last thick bar
- If it is difficult to see, you can hold the pen at an angle.
- If you are unsure whether you have enough insulin remaining for your next dose, discard this OptiSet and start a new one.

Example:
If you have set the dose arrow to 30 units **(B)** and the injection button can only be pulled out to as far as 12 units **(C)**, then only 12 units of insulin can be injected with this pen.



In this example, either the other 18 units will have to be injected using a new pen, or the entire 30 units dose will have to be injected using a new pen.



TROUBLESHOOTING

Wrong dose selected	• If you have pulled out the injection button: Never correct the dosage selector while the injection button is pulled out. This will damage OptiSet. Press the injection button in completely to discard the dose and select again. • If you have not yet pulled out the injection button: you can still change the dose by turning the dosage selector to the right or left.
Dose has been selected and the injection button has been pulled out and pressed in again without a needle attached	1. Attach a new needle 2. Press in the injection button completely in and discard the insulin. 3. Perform the safety test. If the safety test is successful OptiSet is ready for use. If test is not successful, the pen might be damaged. Use a new OptiSet. If in any doubt whether the pen is working correctly use a new OptiSet
The amount indicated on the injection button is lower than the dose selected	There is not enough insulin in the reservoir, see section **"Checking the reservoir for remaining insulin"**.
The amount indicated on the injection button is more than 2 units higher than the dose selected	OptiSet is damaged, use a new OptiSet
The injection button cannot be pressed.	1. Make sure you pulled the injection button out completely. 2. Check if needle is attached properly or if needle is blocked. 3. Attach a new needle 4. Push the injection button completely in to discard the insulin. 5. Perform the safety test.
You don't hear clicking while injecting	OptiSet is damaged, use a new OptiSet
Insulin is leaking from the pen	Needle has been attached imprecisely (e.g. at a slant). Remove needle and replace with a new needle putting it on straight. Perform the safety test.
Air bubbles are present in the reservoir	Small amounts of air may be present in the needle and insulin reservoir during normal use. You must remove this air by performing the safety test. The tiny air bubbles in the insulin reservoir that do not move with gentle tapping will not interfere with the injection and dosage.
OptiSet is damaged or is not working properly	Do not force it. Do not try to repair nor use tools on it. Use a new OptiSet.
OptiSet has been dropped or subjected to impact	If in any doubt whether the pen is working correctly use a new OptiSet.